1 **NIH Chronic Graft versus Host Disease Research**

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2 **No Relevant Financial Relationships with Commercial Interest**

List of Non-FDA Approved uses
All treatments discussed for cGVHD

Objective:
Review cGVHD etiology and manifestations and discuss unique approaches to studying and treating a rare disease at the NIH.

3 **Introduction**

- Transplant as a treatment option
- Brief review of acute GVHD
- Chronic GVHD
  - Risk Factors, incidence, manifestations
  - Prevention
  - Standard Treatment
- cGVHD Research at NIH
- Limitations in cGVHD Research
- Future directions

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7 **Choosing a donor**

- Autologous = Patient's stored cells
  - No GVHD
- Syngeneic = Identical twin
  - No (significant) GVHD
- Allogeneic = Another person
  - Related HLA identical match (Genotypic match)
  - Unrelated HLA match (Phenotypic match)
  - Haploidentical +/- phenotypic matching (parent)
  - Mild to severe GVHD

8 **Stem cell sources**

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10 **Preparation or conditioning for transplant**

- Destroy malignant cells
- "Turn off" the immune system to promote engraftment
- Provide milieu for normal cells to grow
- Conditioning regimen depends on patient
  - Myeloablative
  - Non-myeloablative or RIST
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11 **Myeloablative versus Non-myeloablative**

12 **Transplant as a treatment option**

13 **Prevention of GVHD**

- Medications given to prevent GVHD
  - Prednisone
  - Cyclosporine
  - Cytoxan
  - Antithymocyte Globulin (ATG)
  - Methotrexate
  - Tacrolimus (FK506)
  - Mycophenolate mofetil (MMF)

14 **Categories of Acute and Chronic GVHD**

- Classic Acute
  ≤ 100 days Acute features
- Persistent , Recurrent or Late Acute
  >100 days Acute features
- Acute/Chronic Overlap
  No time limit Acute and chronic features
- Chronic
  No time limit Chronic features

15 **Acute GVHD Immunopathology**

16 **Development of GVHD after transplant**

17 **Development of GVHD after transplant**

18 **Development of GVHD after transplant**

19 **Acute GVHD**

- Grade II-IV aGVHD occur in 30-50% matched related donor recipients and up to 70% of unrelated donor recipients
- Prevention
  - High resolution typing
  - Preparative regimen, graft manipulation, chemoprevention/immunosuppression
  - MTX, CSA, ATG, prednisone, Cya

20 **Acute GVHD**

21 **Acute GVHD**

22 **Acute GVHD**

- Standard frontline therapy - steroids (prednisolone equivalent 2mg/kg/d)
  - 50%overall response rate.
    - RR 63-95% grade II, 17-39% grade III, and 0-6% for grade IV
- 100 day survival
  - 78-90% grade I, 66-92% grade II, 29-62% grade III and 23-25% for grade IV

23 **Chronic Graft-Versus Host Disease (cGVHD)**

- A multi-system chronic alloimmune and autoimmune disorder which develops within three years after allo-HSCT
  - Features resemble autoimmune diseases and immunodeficiency, immune dysregulation
  - Can result in significant morbidity decreased organ function
- Major cause of late non-relapse mortality
  - Increased risk of life-threatening infections
  - Leading cause of non-relapse mortality > 2 years after BMT

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26 **Chronic Graft-Versus Host Disease (cGVHD)**

- Major cause of late non-relapse mortality

27 **Diagnosis and Staging of cGVHD**
Definition

- Onset
  - Quiescent - aGVHD resolved (intermediate prognosis)
  - Progressive - aGVHD not resolved (worst prognosis)
  - De novo - no aGVHD (best prognosis)
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- Grade – Seattle Criteria
  - Limited - localized skin or hepatic
  - Extensive - generalized skin or localized skin or hepatic with 2nd involved organ system

28 **Diagnosis and Staging of cGvHD**

- Grade - NIH Consensus Criteria
  - Mild - 1 or 2 organs or sites (except lung) with no clinically significant functional impairment
  - Moderate -
    - i) at least one organ or site with clinically significant but no major disability, or
    - ii) three or more organs or sites with no clinically significant functional impairment. A lung score of 1 will also be considered moderate chronic GVHD.
  - Severe - major disability caused by chronic GVHD. A lung score of 2 or greater will also be considered severe chronic GVHD.

29 **NIH cGVHD Organ Score**

30 **Increasing Incidence of cGVHD**

- Older recipient age
- Peripheral blood
- Unrelated donors
- DLIs
- Lower RR mortality
- Treatment of infections

31 **cGVHD Risk Factors**

32 **cGVHD Pathogenesis**

- Poorly understood
- Theories
  - Alloreactive T-cells, aberrant thymopoiesis
  - Altered APC function
  - T-cell imbalance
    - Th2 cells in murine models, Th1/Th2 imbalance
    - ↑TREGs in donor/recipient early = ↓cGVHD)
    - Cytokine dysregulation
      - High IL1-β, IL-6, INFγ, TNF- α, TGF- β
      - Low IL-10
  - Antibody mediated

33 **cGVHD Poor Prognostic Factors**

- Thrombocytopenia (platelets < 100k)
- Progressive onset
- Generalized skin involvement
- Hyperbilirubenemia, cirrhosis
- Low Karnofsky score
- Recurrent infections
- GI involvement (diarrhea, weight loss)
- Steroid refractory disease

34 **Cutaneous cGVHD: A Polymorphous Disorder**

- Epidermis
  - Papular
  - Lichen planus-like
  - Papulosquamous
  - Poikiloderma
  - Keratosis pilaris-like
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- Dermis
  - Lichen-sclerosus-like
  - Dermal sclerosis

- Subcutaneous
  - Subcutaneous sclerosis
  - Fasciitis

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39 **Lower extremity sclerosis**

40 **Ulceration**

1 • Full thickness loss of skin (not erosion)
- Largest ulcer
- Record longest diameter

41 **Schirmer's Test**

- Measurement of tear function (in mm)
  - Without anesthetic: measures both reflex and basal tear function
  - With anesthetic: measures basal tear function

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44 **Obliterative bronchiolitis**

45 **Infections**

- Immune function recovery is variable and depends on several factors; stem cell source, GVHD, and immunosuppression.
- Patients are considered functionally asplenic and should be on penicillin prophylaxis.
- Immunosuppressed from disease and medication.
- Many patients have barrier breakdown from mucosal involvement.
- (Re)vaccination schedules are variable and relying on a generalized schedule for immunization is not practical. Guidelines can be found: CDC website, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm.

46 **cGVHD treatment**

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47 **cGVHD Systemic Therapy**

- Steroids
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Mycophenolate Mofetil (MMF)
- Sirolimus (Rapamycin)
- Pentostatin
- Thalidomide
- Hydroxychloroquine

- Extracorporeal Photopheresis
- Rituximab (anti-CD20), Etanercept (TNFα blockade), Infliximab (anti-TNFα), Daclizumab (anti-IL2R/CD25)

48 **cGVHD Local Therapy**

- Skin: Psoralen-UVA, topical steroids, topical tacrolimus, photoprotection
- Oral: Topical dexamethasone, tacrolimus
- Eye: Ophthalmic steroids, cyclosporine eye drops, punctal plugs, scleral lens
- GI: Ursodiol, oral budesonide
- Joints and fascia: Physical therapy
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49 **2003: NIH Chronic GVHD Study Group**
"Create a high quality multidisciplinary clinical and research program to address challenges that can be uniquely addressed at the NIH"

- Establishing clinical infrastructure
- Studies of chronic GVHD biology
- Development of new treatments
- Leadership in the field
- 04-C-0281
  – Natural History Study of Clinical and Biological Factors in Patients With Chronic Graft-Versus-Host Disease After Prior AlloHSCT

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52 **04-C-0281 NCI Chronic GVHD Natural History Protocol - Cumulative Accrual/Quarter**
Accrual to Date 250

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56 **Montelukast BOS Phase II Trial Design**

- Stable cGVHD rx regimen for > 3 months
- Montelukast added QHS at approved doses
- Primary Endpoint (6 month):
  – Absolute change of FEV1 % predicted (> 15 %)
  – FEV1 slope change (from baseline)
- Secondary Endpoints:
  – functional, patient reported outcomes
  – cGVHD evaluations
  – 2 year overall survival

57 **BOS Diagnosis- Modified NIH Consensus Criteria**

- FEV1<75% and patient decline in FEV1 > 10% per year
- Absence of infection
- Presence of another cGVHD manifestation
- Evidence of obstruction:
  - FEV1/VC < 0.7
  - RV > 120 or RV/TLC > 120% and air trapping on expiratory CT

58 **Summary of Patient and Response (n=20)**

1 Subject & Symptom

- Age
  - Median 48
  - Range (15-63)1 pediatric
- Gender
  - Women/Men (12/8)
- Ethnicity:
  - 2 AA, 2 H, 1 A, 15 C
- Lung Symptom Score:
  - Mild (0,1): 8
  - Moderate (2): 7
  - Severe (3): 4 (1NE)

2 Lung Disease

- BASELINE: FEV1 % predicted
  - Median 45% (24-73)
  - 12/20 patients < 50%
- 6 month PRIMARY ENDPOINT:
  - 16/16 met criteria for success (< 15% decline in absolute FEV1 % predicted)
  - 31% FEV1 $\geq$ 5% increase
  - 38% stable
  - 31% $\geq$ 5% decline

59 **Preliminary Conclusions**

- Montelukast is safe and well-tolerated in patients with BOS (after HSCT)
- Montelukast stabilizes majority of patients with BOS at 6 months: (14/16) by slope, 16/16 by FEV1 change.
- Montelukast may improve survival of patients with BOS
- Leukotrienes may be involved in the pathogenesis of BOS after HSCT
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60 **Inhaled Cyclosporine (CIS)**

- Phase II open label study
- To evaluate whether CIS can improve or stabilize lung function and QOL in individuals with BO.
- >10 yrs of age – 80 yrs
- Evaluation q 3 weeks to minimum of 18 weeks

- Newly opened
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- Primary Endpoint
  - Clinical improvement in ScGVHD using range of motion assessment of affected joints
- Secondary Endpoints
  - Assess toxicity
  - Establish outcome criteria using multi-modality assessments including MRI; QOL; functional assessments
  - Evaluate biomarkers of disease activity and response: PDGFR α/β, IL13, TGFβ, immune phenotype
  - Response of cGVHD in other affected organs
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67 **Future Directions**

- ECP in Children with cGVHD (POB)
- Autologous Serum Eye Drops – M. Datiles (NEI)
- Phase II - Development of a Pediatric Symptom Scale in cGVHD – L. Weiner (POB)
- Natural History and Pathophysiology of Gastrointestinal Graft-versus-Host Disease (NIDDK)
- Cyclosporin gel injection for ocular cGVHD (NEI)
- Mesenchymal Stem Cells for cGVHD (ETIB)
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68 **Future Directions**

- A Phase I-II Study of Continuous Flow Extracorporeal Photopheresis in Children with Chronic GVHD

69 **Limitations in cGVHD Research**

70 **NCI and NIH Chronic GVHD Study Group**